REMARKS

Upon entry of the foregoing amendment, claims 2-12, 16-22, 25, 26 and 28-38, 42, 43, and 45-52 are pending in the application, with claims 1, 13-15, 23-24, 27, 39-41 and 44 canceled without disclaimer of, or prejudice to, the matter as originally claimed. Although claims 1-27 have been withdrawn by the Examiner under 35 U.S.C. § 121, Applicant has amended method claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims.

Currently, claims 28-38, 42-43, and 45-52 stand rejected under as allegedly being obvious under 35 U.S.C. § 103. Claims 28-38, 42-43, and 45-52 are amended to indicate that the compositions of the present invention are able to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells and that treatment of prostate cancer cells with the compositions of the present invention is more effective than the additive effect of treatment of prostate cancer cells separately with TRAIL and an antiprogestin. Support for the amendment of the claims is found in the specification at page 18, lines 18-27, and Figure 1, describing the synergistic effects of using TRAIL and an antiprogestin. Accordingly, no new matter is added by the amendments to the claims.

The Rejection of the Claims Under 35 U.S.C. 103 is Traversed or Rendered Moot

A. Prima Facie Obviousness

The Examiner rejected claims 28-38, 42-43, and 45-52 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida, B. et al., 1999, Oncology 15(4):793-802 (hereinafter "Bonavida"), Yu et al, 2000, Cancer Res., 60:2384-2389 (hereinafter "Yu"), or Gliniak, B., et al., 1999, Cancer Res., 59:6153-6158, (hereinafter "Gliniak"), in view of Fathy El Etreby et al., 2000, The Prostate 42: 99-106 (hereinafter "El Etreby"), or Kiode, S.S., et al., J. Reproductive Medicine, 1998, 43:551-560 (hereinafter "Kiode").

Applicant again respectfully asserts that the Examiner has not established a *prima facie* case of obviousness. The Examiner apparently cites Bonavida, Yu, and Gliniak as describing the use of TRAIL to induce apoptosis in tumor cells. The Examiner cites the other two references, El Etreby and Koide, as describing that Mifepristone may be used to treat prostate cancer (El Etreby) or other types of cancer (Koide).

Applicant maintains that nothing in the references cited by the Examiner, alone or in combination, describes, teaches, or suggests the combination of TRAIL with an antiprogestin such as Mifepristone as a chemotherapeutic composition. Also, Applicant has amended the claims to describe that the compositions of the present invention are able to treat prostate cancer that includes both androgen responsive and androgen independent prostate cancer cells, and that treatment of prostate cancer cells with the compositions of the present invention is more effective than the additive effect of treatment of prostate cancer cells separately with TRAIL and an antiprogestin. Applicant respectfully asserts that there is no suggestion by the references, either alone or in combination, that combining TRAIL with an antiprogestin would be effective in prostate cancer cells, such as LNCaP cells, that are refractory to treatment by either TRAIL or an antiprogestin, or that the combination of TRAIL and Mifepristone would be more effective than the additive effect of the TRAIL and the antiprogesterin separately applied to the cancer cells.

First, Applicant respectfully asserts there is absolutely no description, teaching, or suggestion in the references that describe using TRAIL to inhibit cancer cell growth (i.e. Bonavida, Yu, or Gliniak), that would suggest that TRAIL may be combined with an antiprogestin, such as Mifepristone, to treat cancer.

The Examiner cites the passage in Bonavida that describes that "there is less than 5% cytotoxicity in prostate cancer cells DU145, PC3 and LNCaP that become resistant to TRAIL, when such cells are treated at high concentration of TRAIL (500 ng/ml), however, a combination therapy of TRAIL with chemotherapeutic drugs could reverse the resistance to TRAIL" as suggesting that TRAIL may be combined with an antiprogestin. Office Action at page 3. Applicant respectfully asserts, however, that Bonavida suggests the use of compounds that can prevent the development of anti-apototic cellular machinery as a means to overcome resistance to TRAIL. See Bonavida at 797, col. 1. Thus, Bonavida suggests the use of TRAIL in combination with cyclohexamide (an inhibitor of protein translation), adriamycin (an antibiotic), or actinomycin D (a terminator of transcription). It is not suggested by Bonavida that a compound that has a hormone receptor-mediated function, such as an antiprogestin, would be expected to prevent the development of anti-apoptotic machinery so as to

overcome a cell's resistance to TRAIL. Thus, Applicant respectfully asserts that Bonavida teaches away from Applicant's invention, and that by reading Bonavida, one would be discouraged from using a second agent of the TRAIL pathway in combination with TRAIL, as Bonavida describes using TRAIL with chemotherapeutics that work by different (and more generalized) biochemical pathways (e.g., actinomycin D, adriamycin, and cyclohexamide).

Also, Gliniak describes the use of TRAIL in combination with a topoisomerase inhibitor to treat colon cancer. Gliniak specifically notes, however, that combining TRAIL with many chemotherapeutic agents, including cisplatin, 5-FU, mitomycin, etoposide, or adramycin, did not result in an enhancement of cytotoxic activity. Thus, reading Gliniak, one would be discouraged from using most chemotherapeutic agents in combination with TRAIL.

Finally, Yu describes that TRAIL can induce cell death in certain androgen-insensitive prostate cancer cells. Still, like Bonavida and Gliniak, Yu, does not describe, teach or suggest a mechanism by which antiprogestins would be able to increase the effectiveness of TRAIL so as to provide greater than additive effects for the induction of cell death.

Koide does not add to the deficiencies of the TRAIL references (i.e., Bonavida, Gliniak, and Yu). Koide describes the use of Mifepristone for treatment of cancers other than prostate cancer. Koide describes that the molecular basis of Mifepristone action is the formation of receptor-progesterone/receptor-mifespristone dimers, which compete with the active progesterone/receptor homodimer, to reduce the effectiveness of the agonist progesterone. Koide at page 553. Thus, Koide suggests that Mifepristone acts in a competitive manner with ligands for the progesterone receptor, and teaches away from Applicant's findings that Mifespristone acts on the TRAIL pathway to sensitize cells to TRAIL.

El Etreby does describes that Mifepristone can exhibits anti-tumor activity in androgen-sensitive and androgen-insensistive cells. Still, El Etreby is primarily concerned with androgen-insensitive prostate cancer cells, and does not describe, teach, or suggest that Mifepristone, or other antiprogestins, may be used to increase the TRAIL sensitivity of androgen-sensitive prostate cancer cells such as LNCaP cells, or that

compositions having this ability may be clinically important. Nor, does El Etreby, in combination with Bonavida, Gliniak, Yu, or Koide describe, teach or suggest that antiprogestins, such as Mifepristone, may act in a synergistic manner with TRAIL, at the level of the TRAIL pathway. Thus, as noted by the Examiner, Mifepristone was believed to work via the progesterone receptor. Office Action at page 5. Thus, there was no teaching or suggestion in the art that antiprogestins could be used to sensitive the cellular machinery of the TRAIL apoptotic pathway.

In contrast to the cited references, Applicant describes compositions that act to sensitize cells to TRAIL by specifically activating the DR4/DR5 death receptor pathway, such that the effects seen with the compositions of the invention (i.e., including TRAIL and an antiprogestin) is greater than that of either agent alone. The Examiner has stated that the limitation of formulating a composition having TRAIL and an antiprogestin so as to induce apoptosis in cells that are resistant to either agent is an intended use for the composition. Office action at pages 5-6. The Applicant respectfully asserts that the formulation of a composition that has TRAIL polypeptide and an antiprogestin to provide a composition having increased efficacy is not an intended use, but a quality of the composition itself that renders the composition as a chemotherapeutic agent that provides surprising advantages of over compositions of the prior art.

Thus, Applicant's specification teaches that not all prostate cancer cells are sensitive to TRAIL (see Figure 1 of Applicant's specification). For example, as taught by Applicant's specification, TRAIL does not result in a significant increase in apoptosis and/or DR5 expression in certain LNCaP androgen sensitive prostate cells. Also, such cells are not sensitive to Mifespristone at the levels used by Applicant (see the specification, FIG. 1A, 1C). As described in Applicant's specification, both TRAIL and Mifespristone act via death domain receptors DR4 and DR5 to stimulate of caspase 8, which subsequently activates procaspases 3, 7, and 9. Applicant is therefore able to use Mifespristone to sensitize cells to TRAIL by activating the DR4/DR5 pathway. In this way, Applicant's methods maintains specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway. This is in contrast to the agents proposed by Bonavida and Gliniak which act by much more generalized mechanisms to induce cell death and thus, can result in non-specific side effects. This is also in contrast to the

studies of El Etreby, which suggest that Mifepristone may act to overcome the apoptosis resistance of androgen-independent cells.

The challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Thus, Applicant respectfully asserts that the results of Gliniak and Koide using cancers that are not prostate cancer do not teach or suggest the use of TRAIL with another agent for treating prostate cancer. Nor do the studies of Yu indicate how TRAIL and/or an antiprogestin may be used to treat prostate cancer in those prostate cancer cells that are not sensitive to TRAIL. Nor do the studies of either El Etreby teach how TRAIL may be used to treat prostate cancer cells that are refractory to Mifespristone.

An invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Further, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try." *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levengood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993). Although both TRAIL and Mifespristone had been used individually with some efficacy in treating prostate cancer, there was no indication, based on the results in the cited art, that the combination of TRAIL and Mifespristone would induce apoptosis in prostate cancer cells at a level that is greater than additive for the effects of each agent alone.

Thus, Applicant respectfully asserts that the Examiner has not establishe a *prima facie* case of obviousness under 35 U.S.C. § 103.

B. Secondary Considerations

Without in any way acquiescing that the Examiner has established a *prima facie* case of obviousness, Applicant respectfully asserts that secondary considerations further substantiate that Applicant's claimed composition is not obvious in view of the cited references. Applicant submits herein a declaration under 37 C.F.R. § 1.132 describing why these secondary considerations render the composition patentable under 35 U.S.C. § 103(a).

i. Surprising Results

First, the non-obviousness of Applicant's invention is substantiated in view of the surprising results found by Applicant that: (1) combining TRAIL and an antiprogestin such as Mifepristone is synergistic; (2) that TRAIL and Mifepristone may be used to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells; and (3) that antiprogestins specifically act on the TRAIL pathway .

Thus, Applicant was the first to demonstrate that Mifepristone can sensitize cells to the effects of TRAIL. As described in Applicant's specification, the challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Although Yu describes the use of TRAIL to induce apoptosis in androgen independent cancer cells, Applicant was the first to discover that Mifepristone can increase the efficacy of TRAIL in inducing apoptosis in those prostate cancer cells that are resistant to the apoptic effects of TRAIL. For example, as taught by Applicant's specification, LNCaP androgen responsive prostate cells are not responsive to TRAIL. Treatment of such prostate cancer cells with TRAIL does not result in a significant increase in apoptosis (Figure 1A and 1C of Applicant's specification). Thus, as shown in Figure 1 treatment of LNCaP cells with 400 ng/ml TRAIL does not alter cell survival significantly. Also, such cells were not sensitive to Mifepristone (see e.g., Figure 1A and 1C). However, treatment of LNCaP cells with Mifepristone followed by TRAIL results in a significant decrease in cell survival (Figure 1A and 1C).

Also, as shown by Applicant's specification, the combination of Mifepristone and TRAIL results in effects that are more than additive, but that display synergy. Thus, as shown in Figure 1A , for LaNCaP cells at 16 h, the combination of Mifepristone plus TRAIL results in a substantially greater reduction in survival (down to 40% survival or 60% cell death) than the individual reduction for TRAIL (down to 80% survival or 20% cell death) plus Mifepristone (> 95% survival or < 5% cell death). Similar results are seen for the measurement of apoptosis using the Apoptosense assay (Figure 1C) that measures cytokeratin exposed as a result of apoptosis. Thus, after 16 hours, the measured levels of cytokeratin 18 for the combination treatment of TRAIL and Mifepristone was

about 2.9 units (U) cytokeratin 18 per μg total protein, whereas individually, TRAIL resulted in about 0.6 U/μg and Mifepristone resulted in about 1 U/μg.

Applicant respectfully asserts that there is nothing in the cited references that teaches or suggests the surprising synergy exhibited by the combination of TRAIL and Mifespristone, or that the combination of TRAIL and Mifespristone would be effective to treat prostate cancer cells that are refractory to TRAIL alone. For at least the above reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

ii. Long-Felt Need

Also, the composition of Applicant's invention provides a means to kill both androgen-sensitive and androgen-insensitive prostate cancer cells. By providing a composition utilizing low doses of TRAIL and an antiprogestin, potentially toxic effects of either compound are avoided. Prostate cancer, is one of the most commonly diagnosed malignancies in men, and a leading cause of cancer-related death. Prostate cancer is a multi-focal disease with clones of androgen-sensitive and androgen-refractory cells existing in a cancer. Although androgen depletion therapy often results in regression of the tumor, a small number of androgen-dependent prostate cancer cells are often able to develop into androgen-independent cells. Thus, there is a need to be able to target both types of cells, androgen-sensitive and androgen-insensitive, so as to prevent the less invasive and less metastatic androgen sensitive cells from developing into androgen insensitive cells. Although both TRAIL and Mifepristone had been used to reduce proliferation of prostate cancer cells, Applicant's invention provides a means to more effectively kill both androgen-sensitive and androgen-insensitive prostate cancer cells, using reduced doses of TRAIL and Mifepristone, than either agent alone.

Rejoinder of Withdrawn Claims

Withdrawn process claims that depend from, or otherwise include all of, the limitations of an allowable product claim may be rejoined in accordance with the provisions of MPEP § 821.04, and such amendments will be entered as a matter of right if presented prior to allowance. Applicant has amended claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims. Applicant respectfully asserts that as

amended, the withdrawn claims are in a form suitable for immediate allowance, and request reentry of the amended method claims 2-12, 16-22, 25 and 26 into the application.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

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